Title: Inflammation and premature aging in advanced chronic kidney disease

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Abstract

Systemic inflammation in end-stage renal disease (ESRD) is an established risk factor for mortality and a catalyst for other complications which are related to a premature aging phenotype, including muscle wasting, vascular calcification and other forms of premature vascular disease, depression, osteoporosis and frailty. Uremic inflammation is also mechanistically related to mechanisms involved in the aging process, such as telomere shortening, mitochondrial dysfunction, and altered nutrient sensing, which can have direct effect on cellular and tissue function. In addition to uremia-specific causes such as abnormalities in the phosphate- Klotho axis, there are remarkable similarities between the pathophysiology of uremic inflammation and so-called "inflammaging" in the general population. Potentially relevant, but still somewhat unexplored in this respect are abnormal or misplaced protein structures as well as abnormalities in tissue homeostasis, which evoke danger signals through damage associated molecular patters (DAMPS) as well as the senescence associated secretory phenotype (SASP). Systemic inflammation, in combination with the loss of kidney function, can impair the resilience of the body to external and internal stressors by reduced functional and structural tissue reserve, and by impairing normal organ crosstalk, thus providing an explanation for the greatly increased risk of homeostatic breakdown in this population. In this review, the relation between uremic inflammation and a premature aging phenotype, as well as potential causes and consequences are discussed.

Introduction

End-stage renal disease (ESRD) is characterized by a greatly increased risk of cardiovascular and infectious mortality, as well as by structural and functional abnormalities of various organ systems, most notably the cardiovascular, the immune, and the musculoskeletal system. Substantial similarities in phenotype exist between ESRD and the aging process. About 30-50% of pre-dialysis, hemodialysis (HD), and peritoneal dialysis (PD) patients have serologic evidence of an active inflammatory response that is related to adverse outcomes (17, 18, 132). Persistent "uremic[i] inflammation", as this phenomenon has been coined in the literature (148), resembles that observed in various chronic diseases as well as in the aging process in the general population ("inflammaging"). (68, 137).

Although several reviews already have addressed the causes and nature of uremic inflammation in detail (18, 60, 132), recent findings have revealed novel causes and mechanisms of uremic inflammation as well as the catalytic role of systemic inflammation changing the risk factor profile. Since systemic inflammation may be both a cause and consequence of (premature) aging this may be of relevance for the marked discrepancy between chronological and biological age observed ESRD (68, 137). The aim of this review is to discuss potential similarities between the pathophysiology of inflammaging and systemic uremic inflammation, as well as on the putative relation between uremic inflammation and premature aging.

Mechanisms of uremic inflammation

Premature aging of the immune system

The immune system is a complex orchestration of cells, cytokines and other molecules that act in a paracrine, autocrine, or endocrine manner to protect the human organism primarily against infectious disease (114). Whereas this mechanisms is essential for survival, when chronically

78 stimulated, it can become maladaptive and is in this sense an example of antagonistic pleiotropy
79 (142). In the uremic milieu, abnormalities in the immune response are characterized by an abnormal
80 activation *and* a reduced functioning of components of the innate and adaptive immune system,
81 which contributes to systemic inflammation and increased susceptibility for infectious complications
82 (58). Various abnormalities, such as an impaired neutrophilic phagocytic capacity, depletion of B-cells
83 and naïve T-cells as well as depletion of dendritic cells contribute to reduced functioning of the
84 immune system ("immunosenescence") (8, 58, 155). Important similarities exist between the
85 effects of aging and ESRD on the adaptive immune response (8, 9), whereas a comparable systemic
86 activation of the innate immune response may also be observed during aging ("inflammaging") (68).
87 Both factors argue for a premature aging process of the uremic immune system (9).

88 *Activation of the innate immune system*

89 The activation of the *innate* immune system in uremia is characterized by an increase in pro-
90 inflammatory cytokines, such as TNF and interleukin (IL)-6. Activation of transmembranous Toll-like
91 receptors (TLR4), classically by pathogen-associated molecular patterns (PAMPS), induces
92 transcription factors, such as nuclear factor-κB (NFκB) (89, 96), which is a master regulator of
93 cytokine secretion. Moreover, IL-6 stimulates hepatic C-reactive protein (CRP) production (28).
94 Importantly, NFκB is also upregulated by oxidative stress, and can be stimulated by cytokines, such as
95 TNF, leading to self-stimulation of the inflammatory process (116) [Figure 1].

96 NLPR (NACHT, LRR and PYD domains-containing protein) inflammasomes form another class of
97 pattern recognition receptors (PRR). These lead to upregulation of IL-1B and IL-18 expression through
98 caspase 1. Inflammasomes are intracellular protein complexes, which are activated by a variety of
99 triggers, including cytokines, reactive oxygen species (ROS) as well and damage-associated molecular
100 patterns (DAMPS) (76) [Figure 1]. An increase in NLRP3 mRNA expression, as well as upregulation of
101 caspase 1, IL-1B and IL-18 was observed in peripheral blood mononuclear cells of HD patients

compared to controls (42). Whereas circulating myeloid cells and M1 macrophages are the primary effector cells of uremic inflammation (42), the inflammatory response can also be triggered in other cell types, such as vascular endothelium and vascular smooth muscle cells (14, 42, 89, 147).

Defective regulation of the inflammatory process

The inflammatory process is, under physiological circumstances, meticulously regulated, with an intricate balance between pro- and anti-inflammatory parameters (135). For the regulation of innate immune system, the sirtuin family, and most notably Sirtuin-1, plays an important role, modulated by Nf-kB inhibition through different pathways, such as AMPK, PGC-1α and PPAR (160). Sirtuin-1 down-regulation may also lead to an imbalance between M1 pro-inflammatory and M2 anti-inflammatory macrophages in favor of the former. Sirtuin-1 downregulation has been observed in aging and metabolic syndrome and relates to inflammatory markers (59). Reduced sirtuin 3 expression also relates to mitochondrial damage and increased oxidative stress in animal models of acute kidney injury (102). Noteworthy in this context are recent observations indicating that at least two miRNAs (hsa-mir-217 and hsa-mir-125b) regulate sirtuin and AKT activity, as well as the mTOR pathways involved in regulating aging processes across taxa (91), providing a biochemical link between cellular ageing, stress and damage responses. Although its role in the pathogenesis of uremic inflammation needs to be established hsa-miR-125b is a critical component of a range of immunological phenomena, including host-defense responses, autoimmunity, immune cell differentiation and IL-4 and INF-γ expression (145). A study using genome-wide gene expression profiling identified a differential expression of 80 genes between 10 hemodialysis (HD) patients and controls; variations of these genes are linked to pro-inflammatory pathways, such as the TLR pathways. Using interaction network analysis, 68 differentially expressed miRNA were connected to 47 genes suggesting an important role for miRNA in the regulation of uremic inflammation (170).

Arguments for a premature aging process in ESRD in relation to systemic inflammation

The first argument for an uremic premature aging process is the increase in age-adjusted mortality, which is an aspecific marker of ageing. A recent editorial argued against the indiscriminate use of the term premature aging and proposed four domains of the aging phenotype (87) i.e. 1) changes in body composition, 2) impaired energy balance, 3) impaired homeostatic mechanisms and 4) neurodegeneration. A reduced lean tissue mass mass and an increase in fat mass (sarcopenic obesity) have been reported in ESRD (85, 86); both relate to the expression of inflammatory markers (50). A low bone density is another prevalent feature of ESRD that relate to inflammation and adverse outcomes (22). Regarding energy balance, both maximum aerobic excercise as well as tissue glucose uptake are reduced in CKD (20, 153). While energetic efficiency appears to be reduced, resting energy expenditure are increased in ESRD, in relation to inflammation (158). Also, there is an inverse relation between physical activity (or physical capacity) with inflammatory markers (33).

Except from anemia with high erythropoietin, the impaired homeostatic mechanisms mentioned by Margolick and Ferrucci (87) are all prevalent in uremic inflammation (68, 137). Notably, in keeping with these feautures, neurodegeneration, impaired cognitive function and balance are already prevalent in earlier stages of CKD (44, 88), whereas brain atrophy is a well known complications of ESRD (32). Next to these four domains, vascular progeria is a common finding in the inflamed uremic phenotype and significant associations between vascular calcification and increased vascular stiffness with inflammatory biomarkers are often reported (68). Thus, according to the phenotypic criteria, it can be concluded that an argument for the presence of a premature aging syndrome can be well made. Moreover, recent studies found that abnormalities in the kidney and blood vessels in patients with renal failure were associated with a progeric and senescent phenotype (138, 143).

Mechanistic relations between uremic inflammation and (premature) aging

149 The next question is whether uremic inflammation is mechanistically related to biological ageing
150 (174). For this purposes, a reflection on the relation between uremic inflammation and aging
151 hallmarks is relevant (80). In non-uremic mice, chronic inflammation, induced by the knockout of the
152 NFκB subunit 1, resulted in telomere shortening and a phenotype of progressive aging (56). In dialysis
153 patients, increased *telomere attrition* was observed in comparison to age-matched controls and
154 related to inflammatory markers (19, 24, 68). *Oxidative stress*, generally regarded as a major
155 contributor to biological ageing, is increased in ESRD and reciprocally related to (uremic)
156 inflammation (140, 172). Uremic inflammation impairs *nutrient sensing*, which is also considered an
157 important hallmark of aging (80). TNF and IL-6 induce catabolism by stimulation of the ubiquitin
158 proteasome complex and blunt anabolic pathways by IGF resistance and abberrant mTOR regulation
159 (39, 68, 135). These effects, which can be considered a cellular stress response, can explained both
160 by a direct effect of inflammation on these pathways. An alternative explanation is reduced energy
161 availability to the cell because of shifting of energy to the inflammatory response and a concomitant
162 increase in sympathetic nervous system activity (142). Moreover, systemic inflammation is also
163 related to a *decrease in endothelial progenitor cells* in uremic patients (49). This might play a role in
164 impaired vascular repair, although in the same study no link between endothelial progenitor cells
165 and endothelial dysfunction was observed (106). A recent study by Kramann et al (70) show that
166 critical adventitial progenitors (Gli1+ cells) may be relevant therapeutic targets for mitigation of
167 vascular calcification. Senescence may also make the cell more susceptible to damage evoked by
168 uremic toxins and or oxidative stress (16).

169 **Causes of uremic inflammation**

170 *Abnormalities in mineral metabolism*

171 Abnormalities in mineral metabolism appear to be another important link in the relation between
172 inflammation and progeria (75). In adenine-induced CKD rats, dietary phosphate increased systemic
173 TNF as well as tissue (e.g. in kidney heart and aorta) mRNA expression in a dose dependent matter,

which was prevented by the use of the phosphate binder lanthanum carbonate (166). In CKD4 patients the phosphate binder sevelamer increased fetuin-A, which is a negative acute phase protein and an inhibitor of extracellular matrix mineralization) (139) (45) (15). The mechanisms behind phosphate-induced inflammation may at least be partly dependent upon generation of oxidative stress and activation of NFκB (175). Phosphate may also lead to osteoblast induction of vascular smooth muscle cells (VSMC), which might subsequently release inflammatory mediators especially in combination with a senescent phenotype (7). Indeed, increased serum phosphate levels may drive cellular and physiological senescence (73). A surprising result was observed in a study in uremic rats, where the calcification process of dietary phosphate was actually enhanced by a very low protein diet, and was also associated with systemic inflammation, as evidence by an increase in TNF levels and a decline in fetuin levels (167). Another proof linking phosphate to progeria is a recent study that reports that inorganic phosphate activate the mTOR pathway (57).

Fetuin mediates the formation of calciprotein particles (CPP), circulating colloidal complexes containing calcium and phosphate, which are catabolized by the mononuclear phagocytic system (130) and might lead to a reduction of mineral stress. However, formation of CPP also results in the reduction of circulating and intracellular fetuin levels, with a potential loss of protection against the extracellular calcification and to the transformation of VSMC (128). The calcification propensity of serum, which is inversely reflected by the "maturation time" (T_{50}) of CPPs, of serum was related to all-cause mortality in patients with CKD stages 3-4 as well as in renal transplant recipients (61, 129). It can be speculated that when formation of CPP exceeds clearance, the cytotoxic CPP induce pro-inflammatory cytokines (130).

Defective anti-aging mechanisms

An intriguing relation appears to exist between uremic inflammation and the anti-aging protein Klotho (105). The anti-aging properties of Klotho in endothelial cells were explained by inhibition of NFκB translocation from cytoplasm to the nucleus by stabilisation of the NFκB /IKK complex, which

protected these cells from senescence (13). Klotho expression was reduced by TNF, TWEAK and NFκB activation (101, 142). Next to this epigenetic repression of Klotho gene expression via accumulation of protein bound toxins may be operative (144). As Klotho is also a potent inhibitor of vascular calcification, a self-reinforcing interaction between uremic inflammation, phosphate accumulation, decreased Klotho expression, cellular senescence, and vascular calcification may be operative in the uremic milieu (51).

Gut dysbiosis

The causes of inflammation specifically related to dialysis treatment, such as vascular access, bioincompatibility of dialysis membranes contamination of dialysis solutions or the use of intravenous iron, have been summarized extensively in previous reviews (17, 34, 40) [Figure 2]. The same holds true for potentially modifiable factors, such as periodentitis (17, 40, 71, 72). An emerging factor with relevance for both inflammaging and uremic inflammation is gut dysbiosis (83) (110, 156). Shi et al. (125) observed bacterial DNA in 12 out of 52 ESRD patients and a correlation with CRP and IL-6 levels. Elevated endotoxin levels, which are related to bacterial DNA (125), have also been observed in uremic plasma (93) and soluble CD14 predicts mortality in HD patients (109). Morever, the microbial metabolite Trimethylamine-N-oxide (TMAO), which has been linked to adverse cardiovascular outcome, correlates with uremic inflammation and is an independent predictor of mortality in CKD (99). Although the origin of the increased endotoxin levels in uremia remain to be elucidated it is likely that a translocation of gut microbiome due to increased gut permeability is the primary contributor. Constituents of tight junctions like claudin-1, occludin and ZO-1 were reduced in the colon of uremic rats (157). A recent study showed that depletion of tight junction proteins coincided with a reduction in nuclear factor erythroid 2-related factor 2 (Nrf2), which has a central role in the regulation of intracellular oxidative stress (74). Recently, a study studied the interaction of gut dysbiosis, aging and inflammation. In wild-type mice, the microbial constitution of the faeces, changed with aging whereas gut permeability increased, leading to translocation of bacterial

products into the blood and induction of systemic inflammation. Remarkably, these age-related changes were absent in TNF-α deficient mice, which was explained by an interaction between the inflammatory state of the host and the intestinal microbiome (150)

Regulation of oxidative stress

Uremic toxins such as phosphate, protein bound toxins and advanced glycation end (AGEs) products, can evoke inflammatory pathways directly or mediated by oxidative stress (47). ROS stimulates the inflammatory process through NFκB signaling (78). As the uremic milieu may down-regulate Nrf2 (107), which inhibits NFκB and upregulates a large number anti-oxidative genes (90), impaired Nrf2 activity likely contributes to uremic inflammation. Perturbed expression of these expression factors also appears to contribute to senescence(176).

Non-enzymatic glycation

During the ageing process, increased protein damage takes place as a result of non-enzymatic glycation (108). Protein glycation was viewed originally as a post-translational modification of proteins that accumulated slowly on extracellular and long-lived proteins throughout life. In the extracellular matrix, so called advanced glycation endproducts (AGEs) caused aberrant cross-linking resulting in a decrease of elasticity in vessels leading to arterial stiffness and hypertension, i.e. hallmarks of vascular ageing. The physiological consequences of the formation of AGEs in the aetiology of a range of important age-related diseases, such as ESRD, have been described (82). In addition to the slow formation of AGES, glycation adducts are also formed in a fast manner on cellular and short-lived extracellular proteins and on DNA. The highly reactive methylglyoxal (MG) is a key compound involved in the very fast generation of glycation adducts on proteins, lipids and DNA. Methylglyoxal is mainly generated as a by-product of glycolysis. To counteract the deleterious effects of MG, organisms contain an enzymatic glyoxalase defense system comprised of glyoxalase I (GLO1) and GLO2, in which MG is converted to D-lactate. GLO1 is a key enzyme in regulating the levels of

MGO and AGEs. It has been shown that GLO1 and GLO2 activity decreases in human arterial tissues and red blood cells during the aging process (63, 94). The downstream consequences of GLO1 reduction have been demonstrated by an overexpression of the GLO1 homologue in *C. Elegans*, resulting in an increase of the mean and maximum lifespan by ca 30%; silencing the GLO1 homologue decreased the lifespan by about 50% (100, 122). Thus, since the balance between the production of MGO and its detoxification by GLO1 contribute to the ageing process, managing this balance is important for the prevention of age-related health problems (164). Next to their direct effects on the (vascular) aging process, AGEs can also induce inflammation via NFkB activation and subsequent expression of pro-inflammatory cytokines (141) in target cells, such as VSMC. A relation between serum pentosidine levels and monocyte activation markers was observed in CKD (162). On the other hand, blockade of the RAGE receptor reduced oxidative stress and atherosclerosis in uremic mice, but not the mRNA expression of inflammatory mediators in aortic smooth muscle cells (11). AGEs could also contribute to inflammation by endoplasmatic reticulum (ER) stress (90), which occurs when the demand for protein folding, a major task of the ER, exceeds capacity (31). ER stress may induce inflammation and cellular senescence by NfkB activation and increased translocation of Ca^{2+} into the cytosol (31, 79, 117, 123). It has also been demonstrated that uremic serum induces ER stress in human umbilical vein endothelial cells (HUVEC), via NFkB upregulation (171).

Danger associated molecular patterns (DAMPS)

An important factor in the pathogenesis of inflammaging with potential relevance for uremic inflammation is the presence of misplaced or misfolded molecules, which serve as so-called danger associated molecular patterns (DAMPS), which are non-microbial inducers of inflammation that are evolutionary strongly preserved. DAMPS signal cellular and tissue stress and might evoke an inflammatory response by TLRs, RAGE and/or inflammasomes (38). Various DAMPS have been identified with portential relevance for CKD, such as extracellular ATP, uric acid, S100 proteins and the high mobility group box 1 HMBG1 protein (77, 120). Whereas there is accumulating evidence for a role of DAMPS in the pathogenesis of localized inflammation in CKD (113), the evidence for a role

of DAMPS in the pathogenesis of systemic uremic inflammation is yet limited. However, an inverse relation between renal function and serum levels of HMBG1 (12) and a relation between serum levels of HMBG1 and TNF, IL-6 and CRP (177) have been reported.

Accumulation of DAMPS may be related to a disturbance in *autophagy* (38, 77). Autophagy serves to remove damaged intracellular organelles and to enable the recirculation of essential nutrients. Complex interactions exist between inflammation and autophagy, which may act as a double endged sword for the individual. On one hand, autophagy may eliminate inflammatory triggers by removal of DAMPS. On the other hand, whereas systemic inflammation may induce autophagy through a cellular stress response, autophagy may also release DAMPS and, thus, induce inflammation (77, 118, 119). Similar to oxidative stress and inflammation, autophagy may be beneficial for cellular survival during short-term or minor insults, but have detrimental effects during prolonged or excessive activation. Reduced autophagy was observed in uremic leukocytes (21). However, autophagy of phosphate loaded VSMC was found to be protective against vascular calcification (25). Conversely, in an experimental model of renal failure, inflammation markers were related to increased autophagy in muscle (159). Thus it is not yet clear if increased or defective autophagy is a causative factor in uremic inflammation (161).

Cellular senescence

A factor which is considered highly important in the pathogenesis of inflammaging is the *senescence-associated secretory phenotype* (SASP), in which senescent cells release pro-inflammatory cytokines such as TNF, IL-1, IL-6 and IL-8 (23) (112), which poison the surrounding tissues. The inflammatory process can progress from the cell to the tissue and whole body environment by extracellular spillover and through what is termed the communicome or secretome, which can act at local, tissue, as well as systemic levels. In this communicome, circulating cytokines, miRNA and extracellular vesicles may be involved (38). Senescent mononuclear cells with increased expression of pro-

298 inflammatory cytokines were observed in HD-patients treated with cellulosic membranes, but not in
299 serum of predialysis patients (111). Additionally, phosphate and indoxyl sulphate induce VSMC
300 senescence (103, 165). VSMC in human carotid plaques of non-uremic patients showed evidence of a
301 SASP accompanied by secretion of IL-1a (41). Studies on the SASP in CKD are limited. Although it has
302 been suggested that the SASP is involved in the pathogenesis of chronic allograft nephropathy (131)
303 the role of SASP in the pathogenesis of the uremic phenotype needs to be addressed further. We
304 recently showed that severe uremic arterial calcification was associated with increased vascular
305 expression of *CDKN2A/*^{p16INK4a}, increased number p^{16} positive cells and SASP (138). Notably, in an
306 epidemiological cohort, <10% of the variability in IL-6 expression in the circulation could be explained
307 on the basis of cellular ageing, expressed by telomere length (127). A recent study showed that
308 FOXO4 is elevated in senescent cellls and maintains their viability by preventing p^{53}-induced
309 apoptosis. Inhibition of the interaction between FOXO4 and p^{53} by a modified peptide (FOXO4-DRI
310 [D-retro-invero] resulted in p^{53} induced apoptosis of senescent cells but also improved fitness, fur
311 density and renal function in both naturally aged mice, as well as in a premature aging ($Xpd^{TTD/TTD}$)
312 model (4). Whether substances like FOXO4-DRI could also have an impact on cellular senescence in
313 the uremic phenotype should be investigated in future studies.

314 A special type of cellular senescence, which may contribute to uremic inflammation, is
315 *immunosenescence of the adaptive immune system*. An increase in pro-inflammatory CD4+ CD28-
316 effector cells and an imbalance of the T_{reg}/TH17 cell ratio, simulating immunosenescence, has been
317 detected in uremic serum (8, 26, 173). CD4+ CD25+ FoxP3 T_{reg} cells have an inhibiting effect on
318 systemic inflammation by releasing anti-inflammatory cytokines, such as IL-10 and TGF-β. Since a
319 relation was observed between CRP and IL-6 with and TH17 frequency and an inverse relation was
320 observed between these factors and T_{reg} frequency, a role for T_{reg}/TH17 dysregulation in the
321 pathogenesis of uremic inflammation could be suggested (173). It has also been reported that p-
322 cresyl sulfate induces macrophage activation and interfere in antigen processing, which lead to a
323 failure in the uremic adaptive immune response (3). A consequence of *vascular cellular senescence*,

which could potentially be of major relevance in uremia, is breakdown of the blood brain barrier (168). Potentially, this could contribute to passage of retained cytokines and uremic toxins from the circulation to the brain and promote cognitive dysfunction, anorexia, and depression; all common features of the uremic phenotype (36).

Abnormalities in tissue homeostasis

Abnormalities in tissue homeostasis can also contribute to uremic inflammation following the concept of "para-inflammation" (95). One important potential trigger of uremic inflammation resides in visceral *adipose tissue*. Many ESRD patients show characteristics of "obese sarcopenia"; i.e. a progressive increase in fat mass and a decline in lean tissue mass commonly associated with inflammation (50, 85). The relative increase in (visceral) fat mass may contribute to uremic inflammation (2) via pro-inflammatory adipokines, like leptin and visfatin. However, a recent observational study has actually paradoxically shown a protective effect for higher BMI levels in inflamed, but not in non-inflamed dialysis patients, showing the complexity and reverse causation of pathophysiologic relations that are operative in wasted and inflamed ESRD patients (133).

Abnormalities in fluid or sodium composition of the extracellular tissue could also contribute to uremic inflammation. A relation between extracellular fluid overload and inflammation, as evidenced by CRP or IL-6 levels has been observed in various studies in both HD- and PD-patients (30, 37, 52, 66). Moreover, in accordance with the theory of catalytic effects of inflammation (18) the combined presence of fluid overload and inflammation was associated with a multiplicative risk of mortality as compared to the presence of fluid overload or inflammation in isolation (29). The mechanisms behind the relation between fluid overload and inflammation can theoretically be explained either by increased translocation of endotoxins or gut microbes or microbial fragments across an oedematous bowel wall (i.e. *leaky gut*), or by a progressive decline in lean tissue mass due to sustained inflammation, or by translocation of fluid from the vascular to the interstitial compartments, which may hamper removal during dialysis (29, 55).

There is an accumulation of osmotically interchangeable sodium not only in dialysis patients, but also in patients with non-uremic ageing or uncontrolled hypertension (151). The sodium concentration in this compartment has been estimated to be around 40 mmol/l greater than measured in plasma (10). Accumulation of interstitial sodium may act pro-inflammatory by stimulation of monocytes, and induction of IL-17-producing CD4+ T helper (Th17) cells, which may lead to systemic inflammation (64). In addition, sodium chloride inhibited the activation of IL-4 and IL-13 stimulating M2 (anti-inflammatory) macrophages (10), as well the suppressive function of FOXP3+ regulatory T cells (46). The antibacterial effects of sodium and may be an evolutionary conserved mechanism for antimicrobial skin defense (53). However, whether interstitial sodium accumulation contributes to persistent inflammation and/or has a causal role in the pathogenesis of premature ageing in CKD has not yet been definitely established. A last putative factor contributing to uremic inflammation is *tissue hypoxia*. Studies in healthy subjects have shown activation of the innate immune system, as reflected by an increase in IL-6 and CRP, as well as by an increase in natural killer cells in response to hypoxia (43, 65). Recent evidence indicates that HD-patients suffering from prolonged intradialytic hypoxemia, a condition defined as arterial oxygen saturation levels ≤90% for more than 1/3 of the treatment time, exhibit a pro-inflammatory phenotype (98). Low arterial oxygen saturation, anemia, and low cardiac output are frequently concurrently present in HD patients and may put tissues at an increased risk for hypoxia. Hypoxia triggers adaptive processes in all nucleated cells. HIF-1 mediates the expression of glycolytic enzymes and a switch from oxidative to glycolytic metabolism. This metabolic change results in an increased formation of superoxide, hydrogen peroxide and other toxic ROS (35, 124). HIF regulates an array of processes associated with the immune response and the host response to infection; in particular HIF plays a key role in the activities of T cells, B cells, dendritic cells, macrophages, and neutrophils. Members of the NFκB family regulate inflammation and interact with members of the PHD (prolyl hydroxylase domain)–HIF pathway in ways that link inflammation to hypoxia (121). Taken together, given the pro-inflammatory effects of local and systemic hypoxia and given the novel data there is a distinct possibility that hypoxemia may play a role in the genesis of the

pro-inflammatory uremic phenotype. Emerging data link tissue hypoxia to both mitochondrial dysfunction and inlamed uremic fat (134). Since data from a rodent model of programmed cardiovascular dysfunction link hypoxic pregnancy and oxidative stress to endothelial dysunction, inflammation and premature aging (1) more research is needed in this area. Lastly, *systemic factors* such as depression, as well as socioeconomic and psychosocial factors and associated epigenetic preconditioning, may contribute to uremic inflammation (92), although it is not yet exactly clear to which extent [Figure 1].

Systemic effects of uremic inflammation

Systemic low-grade inflammation is considered to be a cause of premature aging not only in CKD, but also in other chronic diseases such as chromnic obstructive pulmonary disease (COPD), congestive heart failure (CHF), rheumatoid arthritis (RA) and HIV (6, 104, 115, 154). In the previous paragraphs, we have explored to which extent chronic inflammation resembles “inflammaging” in the general population. We outlined how inflammation can contribute to cellular damage as well as activation of cellular stress resistance mechanisms. This can lead to effects in various organ system by a variety of changes, such as endothelial dysfunction, vascular calcification, increased vascular stiffness, left ventricular diastolic dysfunction, osteoporosis, cognitive dysfunction and muscular atrophy (68, 137, 149).

The long-term cumulative effects could lead to various clinical syndromes. The most well known are the malnutrition, inflammation and atherosclerosis (MIA) syndrome (17), and the frailty syndrome [Figure 3], defined by loss of lean tissue mass and muscle weakness as well as a reduced functional capacity, (54). Although the relation between biomarkers of aging and these different phenotypes has not been assessed yet, it is likely that these can be considered a subset of a premature ageing syndrome. Systemic inflammation could also impair the homeostatic balance of the body in various

399 ways. The first is an impaired functioning and reduced structural reserve of cells and vital tissues by
400 direct damage, by mitochondrial dysfunction, or by relocation of free energy for cellular maintenance
401 and repair to the immune system (142, 146). Secondly, systemic inflammation could also impair
402 homeostasis by influencing regulatory networks of the body. Homeostasis depends on a smooth
403 information transfer at all levels; from individual cells to supersystems (163). Systemic inflammation
404 may impair the normal homeostatic fine regulation through the communicome after extracellular
405 spillover of cytokines as well as by an abnormal sympathocovagal balance (38) (152), thus prioritizing
406 the inflammatory response over normal homeostatic regulation, as well as inducing allostatic load.

407 Concluding, systemic inflammation can lead to a reduced structural and functional reserve as well as
408 impaired regulatory mechanisms, resulting in reduced resilience to internal and external stressors.
409 This occurs in combination with the loss of kidney function, which cannot be fully replaced by
410 contemporary dialysis techniques, and with comorbidities. Together, this could provide an
411 explanation for the greatly increased risk of morbidity and mortality in ESRD (67) and, metaphorically
412 stated, for an acceleration of biological time (69, 169).

413

414 **Outlook**

415 Whereas persistent systemic inflammation appears to be a major contributor to adverse outcomes as
416 well as progeria in ESRD, it is not an inevitable consequence of reduced renal function. Indeed, a
417 significant proportion of patients with ESRD have either normal or varying levels of inflammatory
418 markers (97). Next to further investigations of reversible causes of uremic inflammation, it is also of
419 relevance to try to identify patients that are protected from inflammation. Following the example of
420 respiratory medicine (48), “endotyping” of CKD patients, by which detailed phenotypes are coupled
421 to (epi)genetic variants and other biomarkers, could shed more light on both pro-inflammatory as
422 well as protective mechanisms, and their relation to a premature ageing phenotype. There is a great

opportunity for collaboration between basic as well as clinical reseachers on this topic, because, as also shown in this review, the study of uremic inflammation is relevant at all system levels in the body, from (epi)genetics to phenotype. This provides indeed the opportunity to connect these different system levels in order to identify central mechanisms which are ideally also amendable for therapeutic interventions.

However, given the multidimensional causality of uremic inflammation, it is unlikely that a single therapeutic "magic bullet" will ever be identified. Recent reviews (81, 136) summarized five therapeutical concepts, which could be applied to combat inflammation in ESRD. The first is to identify and treat underlying sources of inflammation. The second is to promote healthy dietary habits and lifestyle changes that include low-intensity exercise programs (84). Third, in an experimental setting, pharmacological interventions developed to combat inflammation in other chronic diseases as well as, fourth, anti-cytokine treatments may also be applied in ESRD considered not at increased risk for infectious complications. Finally, as recent data imply that elimination of $p^{16INK4a}$ positive cells improve health span in mice (5), senolytic drugs, such as dasatinab and qurecetin, should be tested in conditions in which senescence may contribute to disease pathogenesis, such as ESRD. Next to interventions specifically focusing on inflammation, it is also of major importance to increase the resilience of the body by physical activity and adequate diet, next to reducing end organ damage due to allostatic overload by factors other than inflammation, e.g. by adequate fluid and blood pressure control and adequate dialysis technique.

Despite the huge potential of the approaches mentioned above (27), few controlled studies have proven success in the management of oxidative stress or systemic inflammation in the uremic milieu. It is of important to realize that targeted mechanisms may have pleiotropic effects (62), or that targeted interventions might focus on pathways, which are influenced by multiple other factors (41). In the future, it is likely that these pitfalls can be partly avoided by the further elucidation of pro- and anti-inflammatory pathways. Since inflammatory biomarkers are "moving targets", randomized

controlled trials need to include large number of patients in each arm in order to provide sufficient power to prove any anti-inflammatory effect of various interventions. Moreover, given the strong interaction between inflammation and the progeric process ("*inflammaging*") it is likely that interventions developed in the gerontology field, or in other chronic diseases will also have relevance for CKD and vice versa (126).

Conclusion

Important conceptual similarities exist between uremic inflammation and "inflammaging" in the general population. The native inflammatory system is based on a highly evolutionary preserved mechanism, which shows a common effector response to a variety of noxious stimuli. In this sense, it also shares important similarities with other chronic diseases, such as COPD, CHF, RA and HIV, although there are clearly disease specific phenotypical differences next to important similarities. It might therefore be hypothesized that uremic inflammation is an example of progressive "unhealthy" aging, both mechanistically as well as phenotypically. Thus, it could be speculated that age-related diseases could be treated more effectively by modulating fundamental mechanisms of aging *per se*, versus the attempt to prevent or delay organ-specific complications one at a time. Studies incorporating patients with different chronic diseases as well as aging subjects may shed more role in the relation between phenotypes and their underlying mechanisms and could provide an answer the question whether phenotypical alterations in these diseases are indeed an example of progressive unhealthy aging. This could in turn lead to shared and better treatment approaches for "inflammaging".

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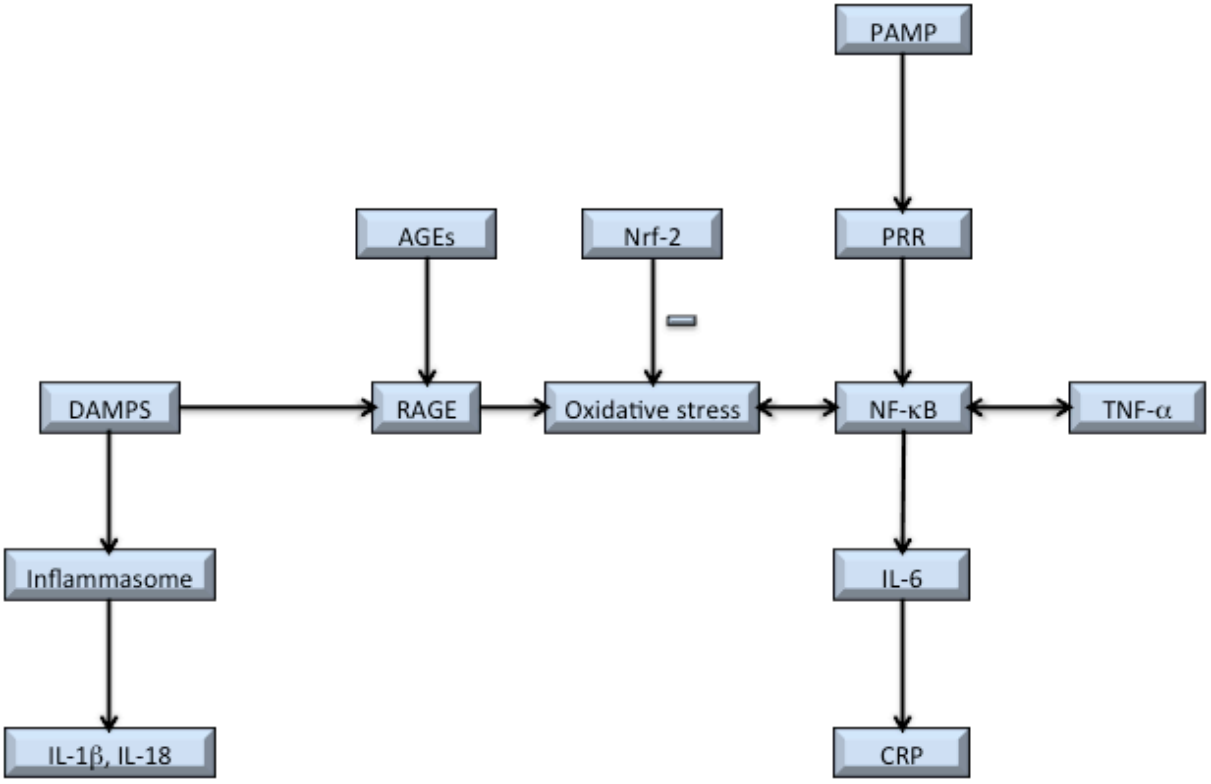
971 **Figure 1. Basic mechanisms of uremic inflammation**

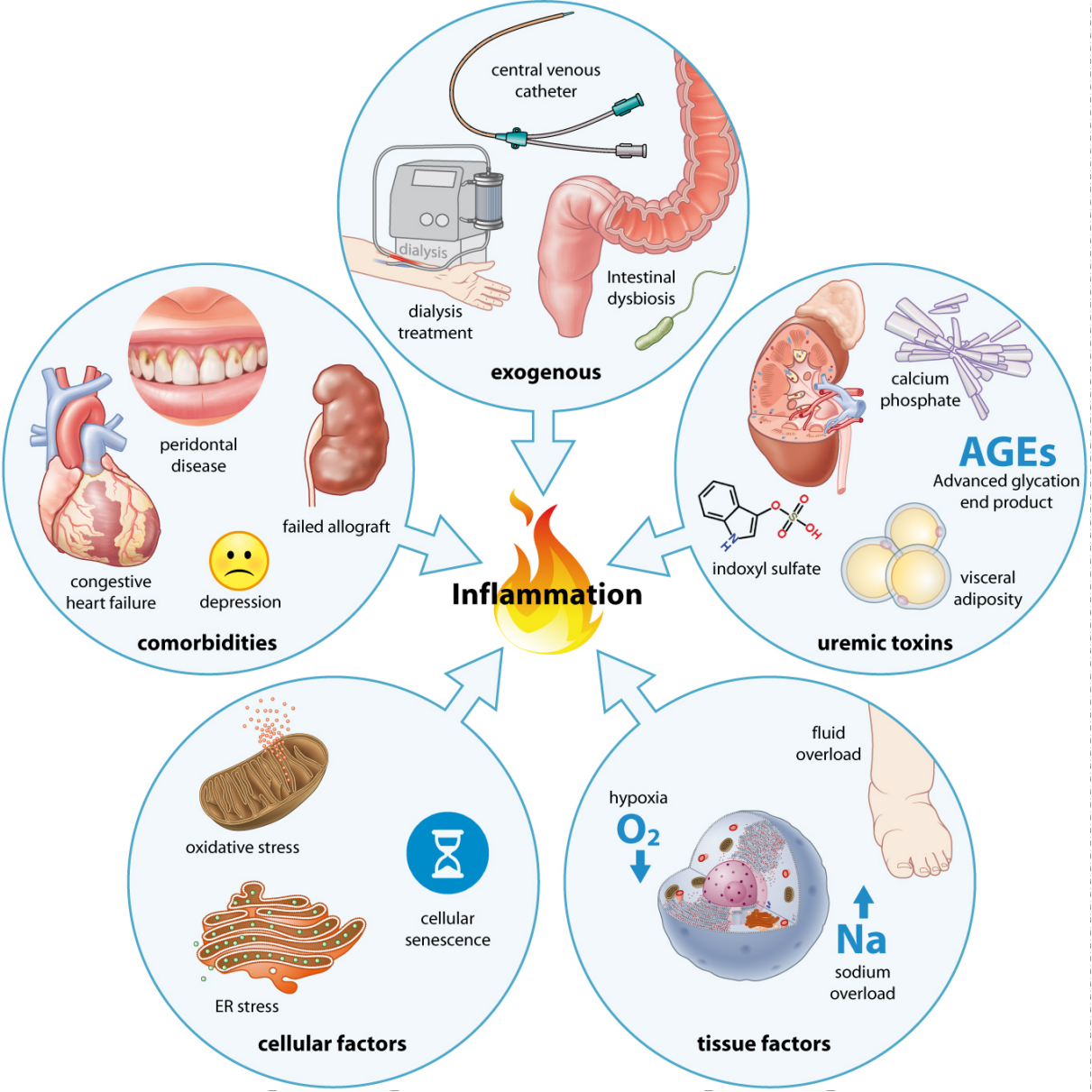
972 **Figure 2. Causes of uremic inflammation**

973 **Figure 3. Inflammation concerns and consequences**

974 **Figure 4. Effects of systemic inflammation on homeostasis**

[i] In which uremia is defined as the medical condition produced by the toxic effects of abnormally high concentrations of nitrogenous substances in the blood as a result of the kidney's failure to expel waste products by way of the urine (https://www.britannica.com/science/uremia)


PAMP
AGEs
Nrf-2
PRR
DAMPS
RAGE
Oxidative stress
NF-κB
TNF-α
Inflammasome
IL-6
IL-1β, IL-18
CRP


central venous catheter
dialysis
dialysis treatment
Intestinal dysbiosis
exogenous
peridontal disease
failed allograft
congestive heart failure
depression
comorbidities
calcium phosphate
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Advanced glycation end product
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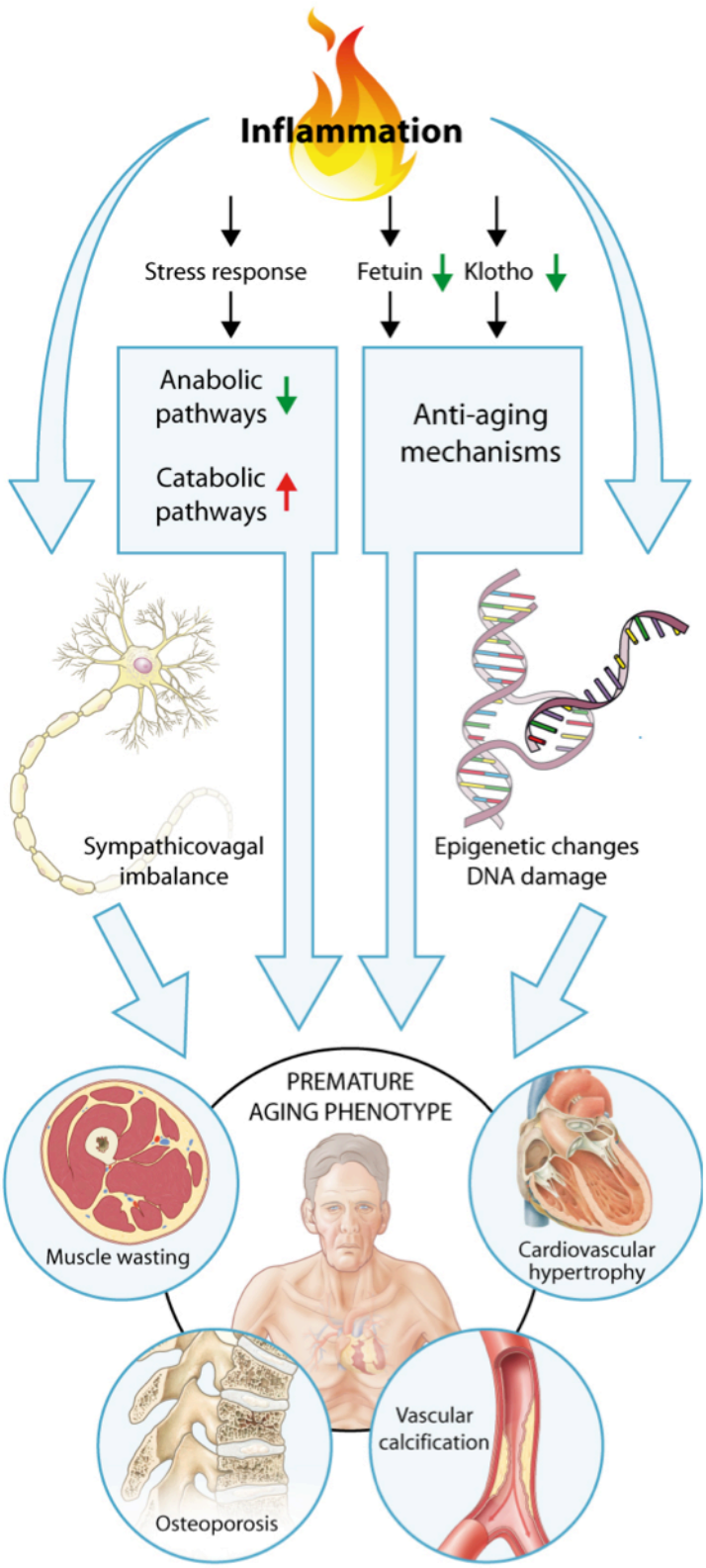
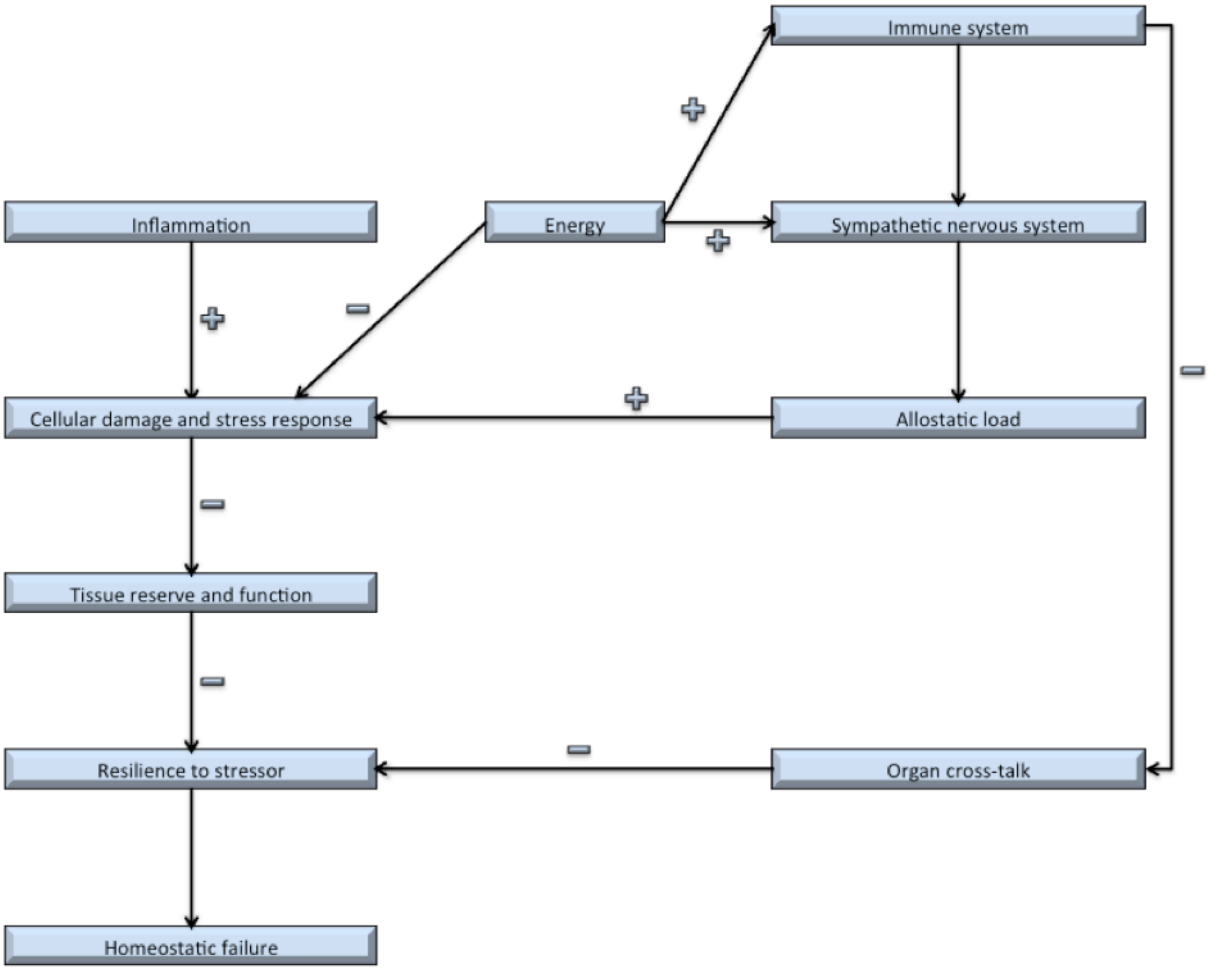

Inflammation
Stress response
Fetuin
Klotho
Anabolic pathways
Catabolic pathways
Anti-aging mechanisms
Sympathicovagal imbalance
Epigenetic changes DNA damage
PREMATURE AGING PHENOTYPE
Muscle wasting
Cardiovascular hypertrophy
Osteoporosis
Vascular calcification


Immune system
Inflammation
Energy
Sympathetic nervous system
Cellular damage and stress response
Allostatic load
Tissue reserve and function
Resilience to stressor
Organ cross-talk
Homeostatic failure